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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/056,230	SCHNITZER, JAN E.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,6-8,10 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 3, 6-8, 10, and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on September 3, 2009 has been entered.

Claims 2, 3, 6-8, 10, and 11 are currently pending and are all amended. It appears claims 2, 3, 6-8, 10, and 11 are all drawn to the same invention and will be examined as such. Claims 2, 3, 6-8, 10, and 11 are currently being examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 2, 3, 6-8, 10, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2 and 3 are unclear with reference to specific components and agents. For example, claims 2 and 3 recite an active agent component, a transport agent component, and a component of caveolae,

therefore the simple reference to "component" in the wherein clause of part a of claims 2 and 3 makes it unclear which component is being referenced. Amendment of the claims to recite "wherein the component **of caveolae** to which" would obviate the rejection.

Further, claims 2 and 3 recite an agent of interest, an active agent, and a transport agent, therefore the simple reference to "agent" in part a and b of claims 2 and 3 makes it unclear which agent is being referenced. Examiner suggests amendment of the claims to recite in part a of claims 2 and 3: "wherein the component **of caveolae** to which the **transport** agent binds and localizes" and in part b of claims 2 and 3: "thereby delivering the agent **of interest**..."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 2, 3, 6-8, 10, and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are drawn to a method of delivering an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner and a

method of delivering an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner comprising selecting an agent of interest that comprises **an antibody or fragment thereof that binds and localizes to a component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface, wherein the component (of caveolae) to which the (transport) agent binds and localizes is lung specific.**

The specification only discloses a monoclonal antibody 833 or TX3.833 that recognizes a 90kDa antigen expressed selectively in caveolae of microvascular endothelium of lung but not other tissues (p. 44), wherein this 833 antibody is the only exemplary antibody shown to function in delivering gold particles or conjugated radioactive agents to the lung endothelial caveolae of rats (p. 45-51). The specification does not disclose any other antibodies that function to bind and localize to any component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface and that are lung specific, deliver an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner, or that deliver an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner as broadly encompassed in the claims.

In the art, Parton et al (Nature Reviews, 2007, 8:185-194) teach that caveolae are made up of numerous proteins, different lipids, including cholesterol and sphingolipids (p. 185, col. 1-2; Figure 1; Box 1 on page 187). Parton et al teach that

defining what constitutes a caveolae is a problem in the art (Box 1, p. 187). Parton et al teach that caveolin proteins from caveolae immunoprecipitate with hundreds of different proteins (p. 191, Box 4). With regards top defining a protein by molecular weight, such as the 90kDa protein that antibody 833 binds, the art recognizes that the molecular weight of a protein does not uniquely identify a protein and is only an estimate of the protein molecular weight and is subject to numerous variables that cannot be readily be predicted, particularly when using gel electrophoresis. Kultima et al (BMC Bioinformatics, 2006, 7:475, internet pages 1-27) teach that gel electrophoresis mainly produces data which enables the investigator to determine whether a particular protein shows an increase or decrease when comparing two different conditions e.g. a diseased state compared to a non-diseased state. The limited dynamic range and poor reproducibility between gels has been of major concern with gel electrophoresis experiments (see 1st para. of Background Section, p. 2). Additionally, Sambrook et al. (Molecular Cloning, 2nd edition, Cold Spring Harbor Press, 1989, p. 18.47) teach that the determination of molecular weight by SDS-polyacrylamide gel electrophoresis is only an estimate and modifications of the polypeptide backbone, such as by glycosylation, can have a significant impact on the apparent molecular weight, see p. 18.47, 1st para. Further, as well known in the art and as taught by the Invitrogen™ product information sheet for protein standards and ladders, the same molecular weight standard may have different mobility and therefor different apparent molecular weights when run indifferent SDS-PAGE buffer systems. Each buffer system has a slightly different pH which affects the charge of a protein and its binding capacity for SDS. Invitrogen™ teaches that one

molecular standard can have very different apparent molecular weights (as much as a 65 kDa difference) depending on the calibration values and buffer systems used (p. 3, last paragraph). The art does not provide any adequate representative species to support adequate written description for the broad genus of antibodies that function to bind and localize to any component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface and that are lung specific, deliver an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner, or that deliver an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner as encompassed by the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of "an antibody or fragment thereof that binds and localizes to a component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface, wherein the component to which the agent binds and localizes is lung specific". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a

recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of antibodies that function to bind and localize to any component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface and that are lung specific, deliver an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner, or that deliver an agent of interest

across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner, per Lilly by structurally describing representative antibodies or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe antibodies that function to bind and localize to any component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface and that are lung specific, deliver an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner, or that deliver an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses antibody 833, this does not provide a description of the broadly claimed antibodies that function to bind and localize to any component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface and that are lung specific, deliver an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner, or that deliver an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific

manner that would satisfy the standard set out in Enzo because the specification provides no structural features coupled to the functional characteristics.

Further, the specification also fails to describe antibodies that function to bind and localize to any component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface and that are lung specific, deliver an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner, or that deliver an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner by the test set out in Lilly because the specification describes only antibody 833. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of a antibodies that function to bind and localize to any component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface and that are lung specific, deliver an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner, or that deliver an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner that is required to practice the claimed invention. Since the specification fails to adequately describe the product to which the claimed method uses, it also fails to adequately describe the method.

Finally, the decision in *In re Alonso* (p. 1-11, submitted for Applicants' convenience) is relevant to the instant claims. In *In re Alonso,* the claims recite a method of treating neurofibrosarcoma in a human comprising administering a genus of

monoclonal antibodies that are idiotypic to neurofibrosarcoma of the human, wherein the monoclonal antibodies are secreted from a human-human hybridoma derived from the neurofibrosarcoma cells. The specification discloses methods for screening for antibodies that are reactive to neurofibrosarcoma cells, however, the specification only exemplifies the production of a single hybridoma HB983 that produces an antibody that functions as claimed. It was concluded that the specification did not provide sufficient support for the broad genus of therapeutic antibodies and one of skill in the art would not conclude that the Applicant was in possession of the claimed genus of compounds. It was further concluded that for purposes of written description, it is not enough to merely disclose the method of making and identifying compounds capable of being used to practice the claimed invention. Disclosure of the single antibody in the specification is insufficiently representative to provide adequate written descriptive support for the genus of antibodies required to practice the claimed invention.

Similarly, the instant application does not provide sufficient support for the broad genus of antibodies that function to bind and localize to any component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface and that are lung specific, deliver an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner, or that deliver an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner by simply describing antibody 833 or disclosing methods of screening for antibodies that bind caveolae,

therefore one of skill in the art would not conclude that Applicants are in possession of the genus of antibodies that function as claimed.

Further, given the claimed antibodies are assumed to bind lung caveolae, there is expected to be great heterogeneity among the antibodies and their antigen-binding characteristics due to the numerous proteins and components of caveolae, hence the specificities of the antibodies falling within the scope of the claimed genus (and the structures of their antigens) would be expected to vary substantially. "A patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated" Noelle v. Lederman (355 F.3d 1343, 1350 (Fed. Cir. 2004) (see page 7 of *In re Alonso*). Given the unpredictable nature of antigen binding for the broad scope of claimed antibodies, the disclosure of antibody 833 or its 90kDa antigen of unknown structure is not sufficient to provide support for the broad genus of antibodies that bind and localize to any component of caveolae of the luminal surface of the lung vascular endothelium upon contact with the luminal surface and that are lung specific, deliver an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner, or that deliver an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner according to the standards of *In re Alonso* and Noelle.

4. Claims 2, 3, 6-8, 10, and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering an agent of interest into and/or across a luminal surface of vascular endothelium in a lung-specific manner **in a rat** and a method of delivering an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a lung-specific manner **in a rat** comprising selecting an agent of interest comprising an active agent component and a transport agent component, wherein the transport agent component comprises **antibody 833,** and contacting the luminal surface of vasculature with the agent of interest, does not reasonably provide enablement for said methods comprising delivering an agent of interest to any luminal surface of vascular endothelium of lungs in *any animal*, wherein the transport agent component comprises *any antibody* or fragment thereof that binds and localizes to *any component of caveolae* of the luminal surface of the lung vascular endothelium upon contact with the luminal surface, wherein the component (of caveolae) to which the (transport) agent binds and localizes is lung specific. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not

'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification discloses a monoclonal antibody 833 or TX3.833 that recognizes a 90kDa antigen expressed selectively in caveolae of microvascular endothelium of lung from rats but not other rat tissues (p. 44), wherein this 833 antibody is the only exemplary antibody shown to function in delivering gold particles or conjugated radioactive agents to the lung endothelial caveolae of rats (p. 45-51).

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for any antibody functioning as claimed other than antibody 833 in rats. One of ordinary skill in the art could not reasonably or predictably extrapolate the disclosure and examples in the specification to the enablement of the claims broadly drawn to **any antibody** that binds to **any component of caveolae** of the luminal surface of the lung vascular endothelium in **any animal** for the reasons below.

With regards to any component of caveolae, Parton et al (Nature Reviews, 2007, 8:185-194) teach that caveolae are made up of numerous proteins, different lipids, including cholesterol and sphingolipids (p. 185, col. 1-2; Figure 1; Box 1 on page 187). Parton et al teach that defining what constitutes a caveolae is a problem in the art (Box 1, p. 187). Parton et al teach that caveolin proteins from caveolae immunoprecipitate with hundreds of different proteins (p. 191, Box 4). Given the great variability of caveolae structure and components and the numerous proteins they can bind and immunoprecipitate with, one of skill in the art would subject to a high quantity of experimentation to determine which component of caveolae the claimed antibody binds in order to function as claimed.

Although the specification discloses that antibody 833 binds a 90kDa protein isolated from rat caveolae, it provides no other distinguishing characteristics of the 90kDa protein. The art recognizes that the molecular weight of a protein does not uniquely identify a protein and is only an estimate of the protein molecular weight and is subject to numerous variables that cannot be readily be predicted, particularly when using gel electrophoresis. Kultima et al (BMC Bioinformatics, 2006, 7:475, internet pages 1-27) teach that gel electrophoresis mainly produces data which enables the investigator to determine whether a particular protein shows an increase or decrease when comparing two different conditions e.g. a diseased state compared to a non-diseased state. The limited dynamic range and poor reproducibility between gels has been of major concern with gel electrophoresis experiments (see 1st para. of Background Section, p. 2). Additionally, Sambrook et al. (Molecular Cloning, 2nd edition,

Cold Spring Harbor Press, 1989, p. 18.47) teach that the determination of molecular weight by SDS-polyacrylamide gel electrophoresis is only an estimate and modifications of the polypeptide backbone, such as by glycosylation, can have a significant impact on the apparent molecular weight, see p. 18.47, 1st para. Further, as well known in the art and as taught by the Invitrogen™ product information sheet for protein standards and ladders, the same molecular weight standard may have different mobility and therefor different apparent molecular weights when run indifferent SDS-PAGE buffer systems. Each buffer system has a slightly different pH which affects the charge of a protein and its binding capacity for SDS. Invitrogen™ teaches that one molecular standard can have very different apparent molecular weights (as much as a 65 kDa difference) depending on the calibration values and buffer systems used (p. 3, last paragraph). Given the known art variability in the methods used to describe the 90kDa protein to which the antibody 833 binds, and given this is the only antibody disclosed that functions as claimed in rats, one of ordinary skill in the art would not predictably be able to identify or distinguish the 90kDa protein from others based on molecular weight, particularly using different standards, different gel electrophoresis conditions or Western blot conditions, hence one of skill in the art could not predictably use the 90kDa polypeptide to screen for and identify antibodies that would function as claimed.

One cannot extrapolate the disclosure of the specification to the scope of the claims functioning in **any animal** other than rats because of the known physiological differences in protein make-up of tissues from unrelated animals, including sequence variability among homologous proteins. Examiner cannot identify and properly assess

the relationship of the 90kDa polypeptide isolated from rat caveolae to that of proteins isolated from any other animals because of the lack of distinguishing characteristics, hence Examiner points to the known variability of protein sequences among homologous proteins of caveolae from different species. For example, Tang et al (J of Biological Chemistry, 1996, 271:2255-2261) provide a sequence alignment between caveolin proteins of rat, chick, mouse, dog, and human (Figure 2) demonstrating sequence variability among the homologous proteins isolated from different species. Even if the 90kDa protein that binds antibody 833 has a homologue in other animal species, given the known sequence variability of homologous proteins between different species, one of skill in the art could not predictably extrapolate the binding of a single antibody 833 that binds to a 90kDa protein from rat caveolae to that of the binding to any component from lung caveolae of any animal, even if homologous, nor could one of skill in the art predictably extrapolate the effects of the antibody to the delivery of an agent of interest to any component of caveolae on the luminal surface of lung vasculature endothelium in any other animal. One of ordinary skill in the art would be subject to undue experimentation to determine which antibody would bind which protein in which animal to predictably function as claimed.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples for the claimed method functioning for any antibody binding any component of lung caveolae in any animal, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 2, 3, 6-8, 10, and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,660,827, Thorpe et al, filed June 1, 1995, as evidenced by Toporsian (Circ Res, 2005, 96:684-692).

Thorpe et al. teach a method of delivering an imaging/diagnostic agent or therapeutic agent/toxin/drug to, into and/or across a luminal surface of vascular endothelium in a tissue specific manner comprising the steps of administering an anti-endoglin antibody, referred to as TEC-4 and TEC-11 (which would be a transport agent component), linked to a radioactive imaging agent or therapeutic agent/toxin (which would be an active agent component or immunotoxin), wherein the anti-endoglin antibody binds to endoglin present on the luminal face of endothelial cells (column 84, lines 33-42 and col. 9, lines 63-67 and col. 10, lines 1-15; col. 6, lines 11-23; col. 44, lines 57-67; col. 45, lines 5-13; Example IV, Figures 17 and 18; Table VI). Antibodies may be conjugated to nucleic acids (col. 45, lines 49-53). As such, Thorpe et al teach delivery of an active agent to, into and/or across a luminal surface of vascular endothelium using a transport agent. Thorpe et al teach the location of delivery can be

to lung tumors or lung tumor vasculature (col. 4, lines 47-54 and lines 60-67). Thorpe et al teach that endoglin is expressed on endothelial cells in lung tumors and normal lung (Tables VI and VII) and the TEC-4 and TEC-11 antibodies can be used to deliver toxins, chemotherapeutic drugs, or radioisotopes because of the highly accessible location of endoglin on the luminal surface of the tumor vasculature (col. 84, lines 43-55). Given endoglin is expressed on lung vascular endothelium, the anti-endoglin antibodies or immunoconjugates taught by Thorpe et al would be lung-specific or deliver agents in a lung-specific manner.

As evidenced by Toporsian, endoglin is present in endothelial caveolae (page 689, 1^{st} column, 2^{nd} full paragraph).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 2, 3, 8, and 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 32, 41, and 42 of copending **Application No. 11/143,114**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending applications are claiming common subject matter. The claims are both drawn to methods of delivering an agent to, into and/or across vascular endothelium in a tissue specific manner, comprising contacting the luminal surface and/or caveolae of vasculature with an agent comprising an antibody, wherein the agent binds a target expressed on the endothelial cell surface, wherein the agent is an imaging or diagnostic agent, and wherein the tissue-specific manner is lung-specific.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 2, 3, 8, and 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 14, 17, and 33 of copending **Application No. 11/143,919**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending applications are claiming common subject matter. The claims are both drawn to methods of delivering an imaging agent comprising an antibody and an imaging or

diagnostic agent component, wherein the antibody binds endoglin (as evidenced by US Patent 5,660,827 above, endoglin is a target expressed on the luminal surface of lung vascular endothelium).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. All other rejections recited in the Office Action mailed February 26, 2004 are hereby withdrawn.

9. **Conclusion:** No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642